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Relationship between alirocumab, PCSK9, and LDL-C levels in four phase 3 ODYSSEY trials using 75 and 150 mg doses

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KEYWORDS:
PCSK9;
Low-density lipoprotein cholesterol;
Monoclonal antibody;
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BACKGROUND: Alirocumab is a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9).

OBJECTIVE: Changes in PCSK9, alirocumab, and low-density lipoprotein cholesterol (LDL-C) levels were assessed after treatment with alirocumab at doses of 75 or 150 mg every 2 weeks (Q2W).

METHODS: Data were analyzed from 4 phase 3 trials (MONO; COMBO II; FH I; LONG TERM); all but MONO enrolled patients on statins. Three trials evaluated alirocumab 75 mg Q2W, with possible dose increase to 150 mg Q2W at week 12 based on week 8 LDL-C; LONG TERM studied alirocumab 150 mg Q2W.

RESULTS: Patients on background statin therapy had higher mean baseline free PCSK9 concentrations vs patients not on statin. After alirocumab administration, increased alirocumab concentrations were associated with dramatic reductions in circulating free PCSK9, resulting in significant LDL-C reductions and a corresponding increase in inactive PCSK9:alirocumab complex. Alirocumab dose increase was associated with a further lowering of PCSK9 and LDL-C. Patients with higher baseline LDL-C levels (>160 mg/dL) were more likely to have their dose increased. LDL-C reductions with alirocumab were consistent between patients with baseline PCSK9 levels above or below the median when the dose increase strategy was used. When started as alirocumab 150 mg Q2W, patients with PCSK9 levels above vs below the median had a greater LDL-C reduction.

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CONCLUSIONS: Alirocumab-induced changes in PCSK9 and LDL-C levels were consistent with the known physiologic relationship between PCSK9, LDL receptor, and LDL-C levels, as well as statin-induced increases in PCSK9 production.

Elevated levels of low-density lipoprotein cholesterol (LDL-C) are associated with increased cardiovascular (CV) risk, and reduction in LDL-C by therapeutic means has been demonstrated to reduce the risk of CV events.[1] LDL-C is cleared from the circulation by LDL receptors on the surface of hepatocytes. The number of available LDL receptors is regulated by proprotein convertase subtilisin/kexin type 9 (PCSK9), which promotes degradation of LDL receptors in the lysosome, thus limiting clearance of LDL-C.[2,3] Monoclonal antibodies that bind to and inhibit PCSK9 lead to an increase in LDL receptor numbers and hence a reduction in circulating LDL-C levels.[3]

Phase 1 and 2 clinical trials of the PCSK9 monoclonal antibody alirocumab confirmed that levels of free PCSK9 (ie, that which is in the circulation and unbound to proteins) are reduced by approximately 7 days after alirocumab administration, corresponding to a marked reduction in LDL-C.[4–6] Levels of total PCSK9 (ie, all circulating PCSK9 including free and protein-bound) were observed to increase after alirocumab administration, representing inactivated PCSK9 bound to alirocumab.

The initial trials in the alirocumab ODYSSEY phase 3 program[7–15] utilized 2 dosing regimens, alirocumab 75 mg every 2 weeks (Q2W), with possible dose increase to 150 mg Q2W depending on achievement of prespecified LDL-C levels, or alirocumab 150 mg Q2W from the outset (note that some later trials used every 4 weeks dosing regimens).[16,17] In a pooled analysis of 8 phase 3 studies, alirocumab 75 mg Q2W (with possible dose increase to 150 mg Q2W at week 12) and alirocumab 150 mg Q2W were shown to reduce LDL-C by 48.6%–60.5% (placebo controls: 0.5%–4.2% increase; ezetimibe controls: 19.3% reduction).[18] However, changes in PCSK9 and alirocumab levels corresponding to LDL-C changes in these phase 3 trials, including data for the 75 mg dose and after dose increase to 150 mg, have not been published. Here we report available data from 4 phase 3 trials that included assessments of alirocumab and PCSK9 levels.

Methods

Studies and patients

This analysis includes 4 phase 3, randomized ODYSSEY trials in which PCSK9 and alirocumab concentrations were measured in addition to LDL-C: MONO (NCT01644474)[7]; COMBO II (NCT02023879)[8]; FH I (NCT01623115)[9]; and LONG TERM (NCT01507831)[10] (Fig. 1). All patients had hypercholesterolemia, with baseline LDL-C levels ≥70 mg/dL (in LONG TERM), ≥100 mg/dL (in MONO), or ≥70/100 mg/dL (depending on history of CV disease in FH I and COMBO II). FH I recruited only patients with heterozygous familial hypercholesterolemia (HeFH), COMBO II and MONO recruited only patients with non-FH, and LONG TERM recruited patients with HeFH or non-FH. Except for MONO, which was conducted without background statin therapy, all trials enrolled patients who had been receiving maximally tolerated statin therapy for at least 4 weeks before study entry. Other additional background lipid-lowering therapies (eg, ezetimibe) were permitted in FH I and LONG TERM.

FH I and LONG TERM were placebo-controlled, whereas MONO and COMBO II were ezetimibe-controlled (Fig. 1). MONO, COMBO II, and FH I evaluated alirocumab 75 mg Q2W, with a possible dose increase to 150 mg Q2W at week 12 if LDL-C remained ≥70 mg/dL at week 8. LONG TERM evaluated alirocumab 150 mg Q2W. Patients received alirocumab treatment for 24 (MONO), 78 (FH I and LONG TERM), or 104 weeks (COMBO II). In all studies, alirocumab was administered subcutaneously using a 1 mL prefilled autoinjector or prefilled syringe. Ezetimibe was given orally, at a daily dose of 10 mg, with or without food (MONO and COMBO II). The studies were performed in accordance with the ethical principles in the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, and appropriate local or regulatory requirements.

Endpoints and laboratory assessments

The primary efficacy endpoint of all trials was percentage change from the baseline in calculated LDL-C at week 24, analyzed in the intention-to-treat population, defined as all randomized patients who had an evaluable primary endpoint, in all 4 studies.

Blood samples were collected in the morning after a 10-hour overnight fast and before study drug administration. All lipid measurements and laboratory tests were assessed by a central laboratory. LDL-C concentrations were calculated using the Friedewald formula (LDL-C = total cholesterol–HDL-C–[triglycerides/5], where all lipid concentrations are in mg/dL). However, if triglyceride values were >400 mg/dL, LDL-C was determined by beta-quantification (such values were not included in the present analysis). Serum samples for total alirocumab and PCSK9 concentrations were collected before dose at week 0 (randomization visit), weeks 4, 12, 16, and 24, and at

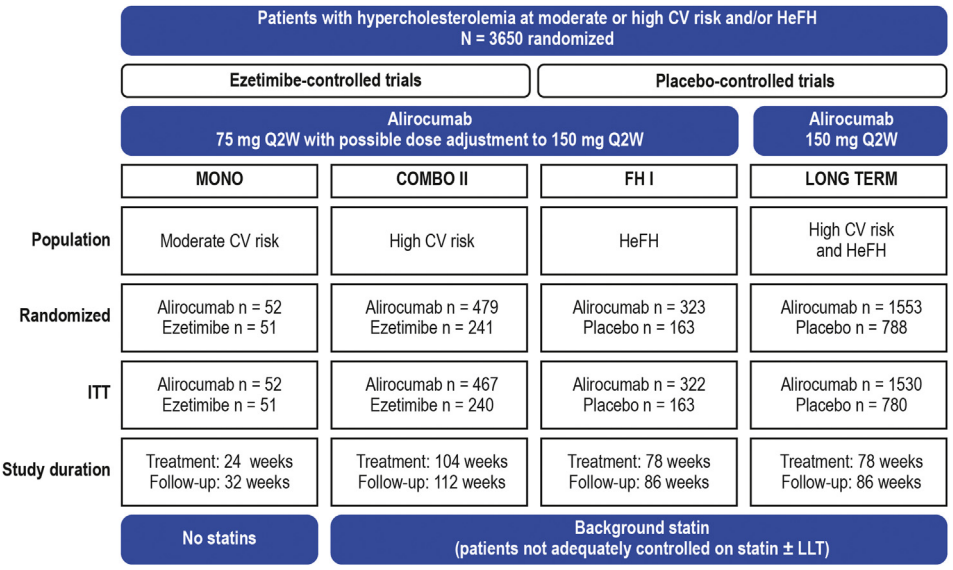

Figure 1 ODYSSEY phase 3 studies and patient populations included in this analysis. Clinicaltrials.gov identifiers: NCT01644474 (MONO); NCT01623115 (FH I); NCT02023879 (COMBO II); NCT01507831 (LONG TERM). CV, cardiovascular; HeFH, heterozygous familial hypercholesterolemia; ITT, intention-to-treat; Q2W, every 2 wk.

the end of the follow-up period, except for LONG TERM study, where samples were collected at weeks 4, 8, 12, and 16, and during follow-up.

Concentrations of alirocumab and total and free PCSK9 were determined by enzyme-linked immunosorbent assay. The method for determining alirocumab concentration included an acid treatment step to dissociate soluble PCSK9:drug complexes present in serum. Alirocumab captured on plates coated with PCSK9 was detected using a mouse anti-alirocumab mAb, followed by a horseradish peroxidase (HRP)-conjugated goat anti-mouse IgG, Fcγ subclass 2b–specific, polyclonal antibody (goat anti-mouse-IgG2b-HRP). A luminol-based substrate specific for peroxidase was then added to achieve a signal. This assay has a lower limit of quantification (LLOQ) of 0.078 μg/mL in undiluted serum. Alirocumab concentrations presented are trough concentrations (assessed 8–21 days after previous injection).

To quantitate free PCSK9 and minimize dissociation of the PCSK9:alirocumab complex in the sample, the assay used a low-affinity anti-PCSK9 mAb, specific for the catalytic domain of PCSK9 as the capture reagent, reduced incubation times, and decreased sample dilution. Standards were prepared in and samples were diluted with PCSK9-depleted human serum. Free PCSK9 captured on the plate was detected using a biotinylated mouse anti-PCSK9 mAb, specific for the pro domain of PCSK9, followed by neutrAvidin-HRP. A luminol-based substrate specific for peroxidase was added to generate a chemiluminescent signal. This assay has an LLOQ of 0.031 μg/mL in undiluted serum.

For total PCSK9 also, standards were prepared in and samples were diluted with PCSK9-depleted human serum. The assay used an acid treatment of the serum samples and standards to dissociate any complexed PCSK9, including any PCSK9:alirocumab complexes that might be present in the serum. The acidified sample was neutralized and all dissociated PCSK9 was captured on a microtiter plate coated with a high-affinity, anti-PCSK9 mAb. PCSK9 captured on the plate was detected using a biotinylated mouse anti-PCSK9 mAb, which noncompetitively bound to PCSK9, followed by neutravidin-HRP. A luminol-based substrate specific for peroxidase was then added to generate a chemiluminescent signal. This assay has an LLOQ of 0.156 μg/mL in undiluted serum.

Treatment emergent adverse events (TEAEs) were defined as AEs that, irrespective of relationship to study drug, developed or worsened or became serious between the first to last injection plus 70 days.

Statistical considerations

Alirocumab, free PCSK9, and total PCSK9 analyses were performed in randomized and treated patients (safety population) with at least 1 evaluable sample after the first injection. Safety analyses were performed on the safety population, defined as all randomized patients who received at least 1 dose or part of a dose of the study drug. Safety data for FH I and LONG TERM (alirocumab vs placebo) as well as those for MONO and COMBO II (alirocumab vs ezetimibe) were pooled for the purposes of this analysis. Percentage change in LDL-C was assessed using mixed effect models for repeated measures to account for missing values.[7] LDL-C concentrations up to week 24 are presented for the intention-to-treat population. Comparison of LDL-C reductions at week 24 for alirocumab vs control according to baseline PCSK9 levels and statin dose intensity were conducted using the mixed effect models for repeated measures. Wilcoxon tests were used to compare baseline PCSK9 levels between groups. No other statistical

comparisons were performed, and data are summarized descriptively.

Results

Patient disposition and baseline characteristics

Across the 4 studies, 3650 patients were randomized (Fig. 1), 2407 to alirocumab arms. Pharmacokinetic samples were collected in 2360 patients randomized to alirocumab.

Baseline characteristics for each trial are shown in Supplementary Table 1. Mean age was 51.9–61.6 years and mean body mass index was 29.3–30.3 kg/m^2. The proportion of male patients varied across the studies. The proportion of patients with ASCVD was 95.1% (COMBO II), 48.4% (FH I), and 76.8% (LONG TERM; no patients had ASCVD in MONO); the proportions with FH were 0% for COMBO II and MONO, 100% for FH I, and 18% for LONG TERM.

Baseline PCSK9 levels are shown in Table 1. In patients on background statin therapy (pooled FH I, COMBO II, and LONG TERM studies), median baseline free and total PCSK9 concentrations were higher (286.0 ng/mL and 647.0 ng/mL, respectively) than those not on background statin from the MONO study (181.5 ng/mL and 475.0 ng/mL, respectively; all $P < .0001$). Furthermore, baseline PCSK9 levels were notably higher in FH I (which included only patients with FH) compared with the other studies.

Patients who received an alirocumab dose increase from 75 mg Q2W to 150 mg Q2W at week 12 had higher mean LDL-C at the baseline compared with patients who remained on 75 mg Q2W (MONO: 153.2 vs 134.7 mg/dL; COMBO II: 140.4 vs 101.1 mg/dL; FH I: 164.9 vs 130.1 mg/dL; Table 2). Most patients who had their dose increased had baseline LDL-C levels >160 mg/dL (Supplementary Table 2). However, baseline free PCSK9 levels were only slightly higher in patients who received dose increase vs no dose increase in MONO and COMBO II and were similar regardless of whether dose was increased in FH I (Table 2).

Changes in LDL-C, free PCSK9, and alirocumab

Changes over time for alirocumab, free PCSK9, and LDL-C for alirocumab-treated patients in the MONO, COMBO II, and LONG TERM studies are shown in Figure 2 (data for FH I are shown in Supplementary Fig. 1). In all studies, by week 4, alirocumab concentrations had increased and free PCSK9 concentrations had reduced, with corresponding marked reductions in LDL-C. LDL-C changes from the baseline to week 24 with alirocumab vs controls were significant ($P < .0001$) in all the trials. Reductions in free PCSK9 and LDL-C were maintained throughout each study. The reductions in free PCSK9 and increases in alirocumab levels also corresponded with increases in the inactive PCSK9:alirocumab complex (represented by total PCSK9; Supplementary Fig. 2).

Treatment with alirocumab 150 mg Q2W in the LONG TERM trial resulted in lower free PCSK9 concentrations (range 42.5–56.8 ng/mL from weeks 4–12) vs the other trials performed with background statin in which all patients were receiving alirocumab 75 mg Q2W up to week 12 (ranges: 118.9–186.1 ng/mL for FH I and 108.2–154.6 ng/mL for COMBO II, from weeks 4–12). Free PCSK9 levels in MONO (no background statin) from weeks 4 to 12 were the lowest of the 4 studies, ranging from 14.9 to 46.1 ng/mL.

LDL-C reductions with alirocumab were consistent between patients with baseline free PCSK9 levels at/above

Table 1 Baseline PCSK9 levels

	Studies on background statins				Studies without statins	*P*-value
Parameter	COMBO II (n = 695)	FH I (n = 479)	LONG TERM (n = 2301)	Pool (n = 3475)	MONO (n = 103)	Studies with vs without statins
Baseline free PCSK9 levels (ng/mL)						<.0001
Number	670	467	2226	3363	102	
Mean (SD)	283.1 (98.8)	314.7 (128.0)	305.0 (121.5)	302.0 (118.7)	185.5 (56.4)	
Median	275.5	292.0	289.0	**286.0**	**181.5**	
Q1: Q3	216.0: 340.0	228.0: 392.0	219.0: 375.0	220.0: 371.0	148.0: 214.0	
Min: Max	0: 704	0: 819	0: 1040	0: 1040	0: 324	
Baseline total PCSK9 levels (ng/mL)						<.0001
Number	671	467	2226	3364	103	
Mean (SD)	620.6 (187.4)	853.6 (293.1)	679.1 (298.8)	691.6 (287.6)	497.5 (154.4)	
Median	592.0	821.0	637.0	**647.0**	**475.0**	
Q1: Q3	492.0: 729.0	637.0: 1040.0	504.0: 805.0	514.0: 820.0	391.0: 594.0	
Min: Max	175: 1430	0: 2040	213: 9030	0: 9030	204: 936	

PCSK9, proprotein convertase subtilisin/kexin type 9; SD, standard deviation.
Note: *P*-value from Wilcoxon test. Bold represents median PCSK9 values in patients receiving or not receiving statin therapy.

Table 2 Free PCSK9 and LDL-C levels by dose increase status*

Study	MONO	COMBO II	FH I
Patients with dose increase, n/N (%)	14/46 (30.4)	82/446 (18.4)	135/311 (43.4)
Baseline free PCSK9, mean (SD), ng/mL			
Patients with dose increase	213.8 (38.3)	295.2 (106.5)	312.5 (144.7)
Patients without dose increase	178.4 (53.6)	271.5 (93.9)	316.5 (120.7)
Baseline LDL-C, mean (SD), mg/dL			
Patients with dose increase	153.2 (24.6)	140.4 (47.4)	164.9 (55.1)
Patients without dose increase	134.7 (26.7)	101.1 (29.7)	130.1 (42.5)
Additional % LDL-C reduction from week 12 to week 24, mean (SD)	−1.4% (8.9)	−10.5% (32.6)	−15.1% (23.8)

LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; SD, standard deviation.
*Alirocumab dose increased from 75 to 150 mg Q2W at week 12 if week 8 LDL-C was ≥70 mg/dL. LONG TERM not included as dose increase was not possible in that study.

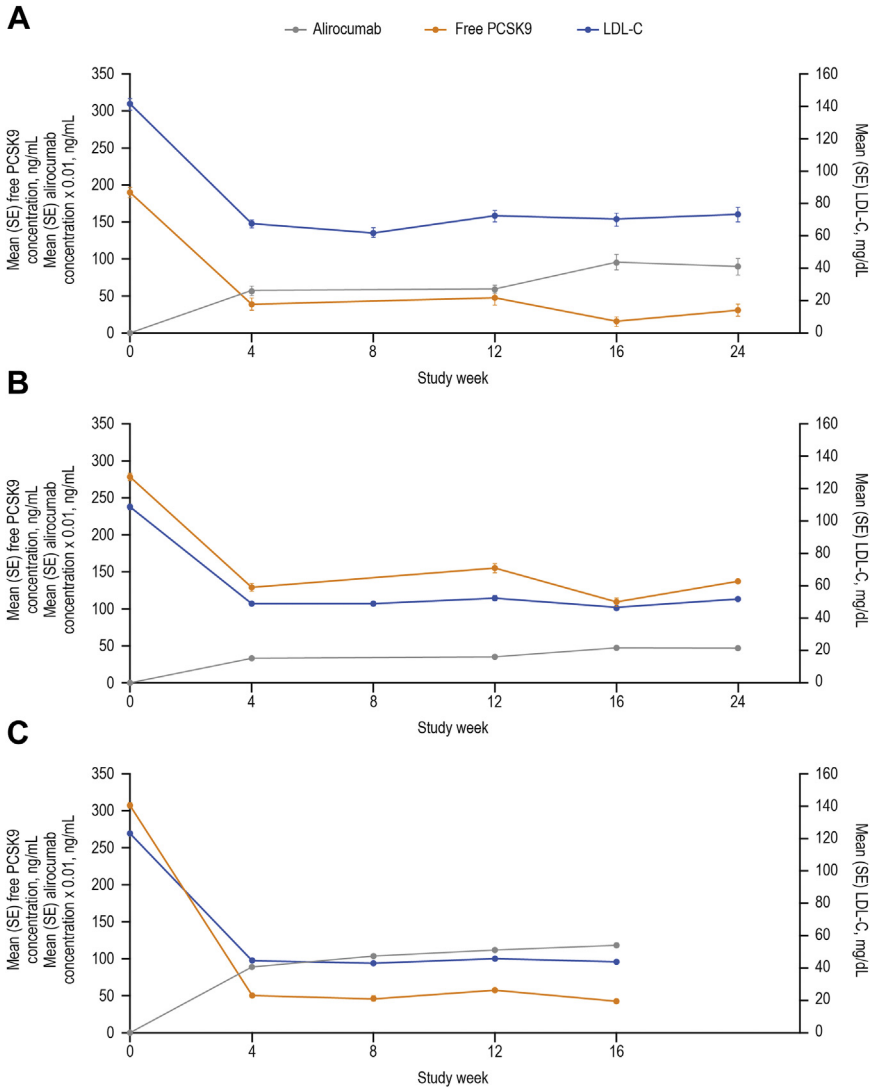

Figure 2 Mean concentrations of alirocumab, free PCSK9, and LDL-C over time in patients receiving (A) alirocumab 75/150 mg Q2W without background statin (MONO); (B) alirocumab 75/150 mg Q2W with background statin (COMBO II); and (C) alirocumab 150 mg Q2W with background statin (LONG TERM). Alirocumab 75/150 mg refers to studies where the starting dose of 75 mg was increased to 150 mg at study week 12 if week 8 LDL-C was ≥70 mg/dL. Alirocumab and PCSK9 samples were available only up to 16 weeks in LONG TERM. LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 wk; SE, standard error.

or below the median in studies where a dose increase strategy was used. When started as the alirocumab 150 mg Q2W dose in LONG TERM, patients with PCSK9 levels at/above the median had a greater LDL-C reduction compared with those below the median (interaction *P*-value = .0076) (Fig. 3). As the interaction *P*-values were calculated using the difference in LDL-C percentage reduction for alirocumab vs control, the LDL-C changes in the placebo group (−0.5% and +2.9% for patients with baseline free PCSK9 below or at/above the median) can at least partially account for the significant interaction *P*-value seen in the LONG TERM study. The LDL-C changes in the alirocumab group in LONG TERM were −59.4% and −62.8% for patients with free PCSK9 below or at/above the median. Similar results were observed when analyzed by quartiles of baseline total PCSK9 levels (Supplementary Fig. 3).

Effect of alirocumab dose increase

The proportion of patients who had their dose increased is shown in Table 2. Changes in alirocumab, PCSK9, and LDL-C levels after dose increase are shown for the MONO study in Figure 4 and for COMBO II and FH I in Supplementary Figures 4 and 5, respectively. Mean concentrations of alirocumab increased in an approximately dose-proportional or slightly greater than dose-proportional manner when alirocumab dose was increased from 75 mg Q2W to 150 mg Q2W.

Similar to the pattern seen at the baseline, at week 12 (before potential dose increase), mean free PCSK9 levels in MONO and COMBO II were somewhat higher in patients who had the dose increase vs no dose increase (59.3 vs 40.4 ng/mL [MONO]; 211.9 vs 141.5 ng/mL [COMBO II], respectively). At week 24, mean free PCSK9 levels decreased further (compared with week 12) in patients who had the dose increase to 14.3 ng/mL in MONO and 131.3 ng/mL in COMBO II (week 24 free PCSK9 levels in patients with no dose increase were 36.9 and 136.7 ng/mL in MONO and COMBO II, respectively). In FH I, mean free PCSK9 levels at week 12 were comparable for patients who received the dose increase vs no dose increase (188.9 vs 185.5 ng/mL) although levels were further reduced to 80.5 ng/mL at week 24 in patients who had the dose increase (compared with 165.9 ng/mL for patients with no dose increase).

The further reductions in free PCSK9 levels after alirocumab dose increase corresponded with additional percentage reductions in LDL-C (week 24 compared with week 12) of 10.5% and 15.1% in the trials with background statins (COMBO II and FH I, respectively); in MONO (no statins), the additional percentage LDL-C reduction was 1.4% (Table 2). At week 24, percentage LDL-C reductions from the baseline in patients with and without dose increase were, respectively, 50.6% and 55.5% in MONO, 42.5% and 54.7% in COMBO II, and 51.5% and 48.9% in FH I. Reductions in week 24 LDL-C ranged from 42.5%–51.5% for those with a dose increase and 48.9%–55.5% for those who remained on 75 mg Q2W.

Effect of statin dose intensity on PCSK9 levels and LDL-C reductions

As noted previously, baseline free and total PCSK9 levels were higher in patients who were receiving a statin vs no statin. We also examined levels of free and total PCSK9 over time according to baseline statin intensity (Supplementary Figs. 6–8). Across the three studies that included patients on background statins, both free and total PCSK9 levels were consistently higher over the course of the studies in patients who were receiving high-intensity statin vs no high-intensity statin. However, we did not find any differences in terms of LDL-C reductions when comparing groups who were receiving high-intensity statin vs no high-intensity statin (Supplementary Fig. 9).

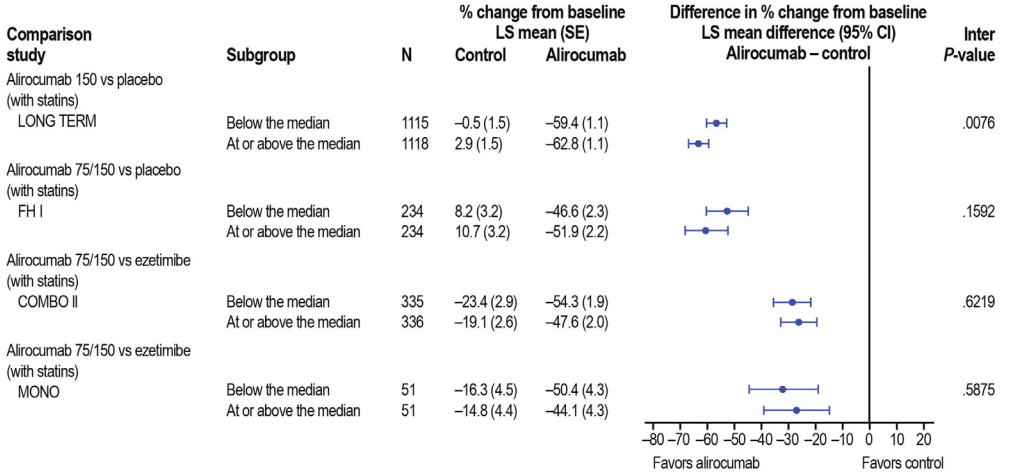

Figure 3 LDL-C percentage reduction at week 24 according to baseline free PCSK9 levels below or at/above the median. CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least squares; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 wk; SE, standard error.

Safety analyses

Pooled safety data from the four studies are shown in Supplementary Table 3. The rates of TEAEs, treatment-emergent serious AEs, and TEAEs leading to discontinuations or deaths were generally similar between alirocumab and control arms. The most frequently reported TEAEs included nasopharyngitis, accidental overdose, upper respiratory tract infection, dizziness, and injection site reaction. TEAEs were generally comparable between alirocumab and control arms, with the exception of a higher rate of injection site reactions with alirocumab. Most injection site reactions, however, were mild in severity. Safety data were also compared between alirocumab and control groups with baseline total PCSK9 levels below or at/above the median (Fig. 5), apart from a few small differences between groups (eg, injection site reactions occurred in 4.6% and 7.5% of alirocumab-treated patients with baseline total PCSK9 levels below or at/above the median, respectively) there was no clear pattern according to baseline total PCSK9 levels.

Discussion

After administration of alirocumab 75 or 150 mg Q2W in the 4 phase 3 trials included in this analysis, increased alirocumab concentrations corresponded with a sharp decrease in free PCSK9 concentrations and an associated significant decrease in LDL-C. These changes were seen by week 4 and sustained through the course of the studies, and results were consistent among patients with HeFH and non-

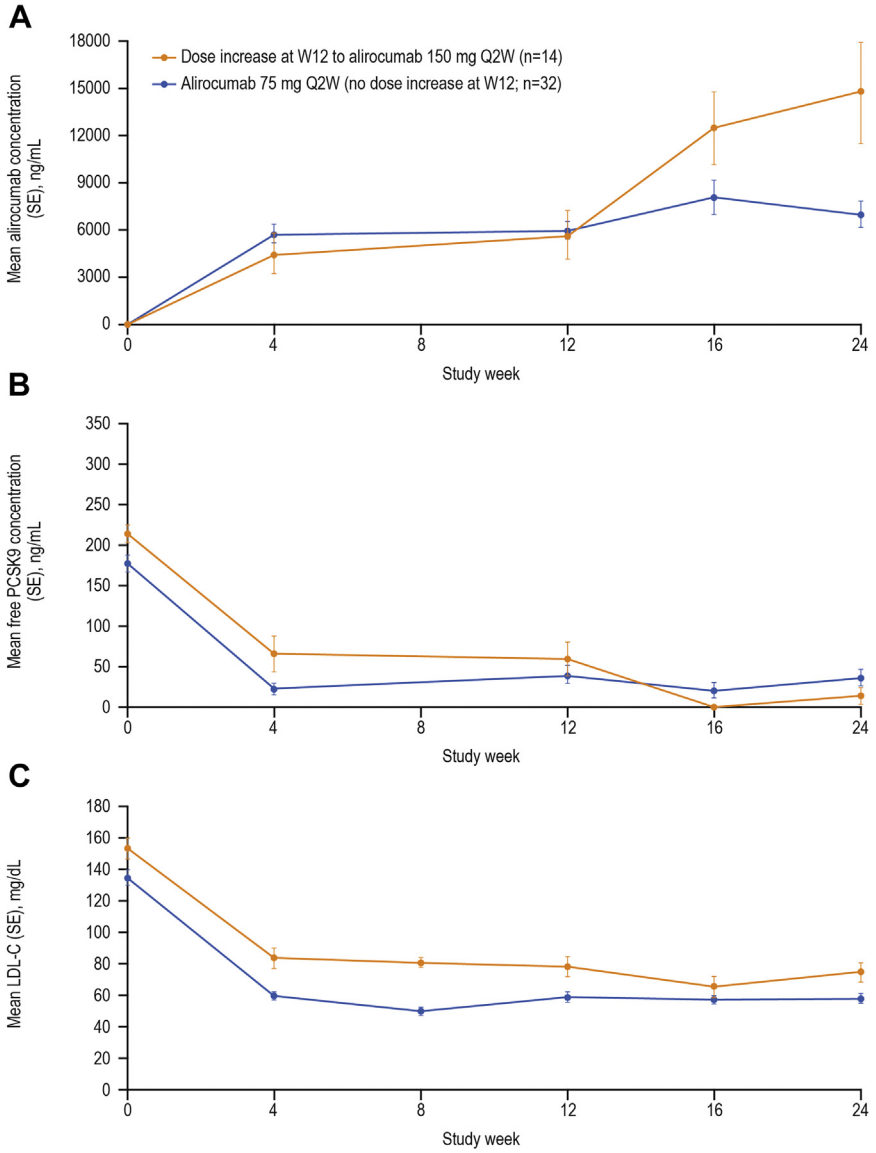

Figure 4 Effect of alirocumab dose increase from 75 to 150 mg Q2W on mean concentrations of (A) alirocumab, (B) free PCSK9 and (C) LDL-C over time, in alirocumab-treated patients from the MONO study (no background statin). LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 wk; SE, standard error; W, week.

TEAEs occurring in ≥5% of patients	Total PCSK9 below median (BM) or at/above median (AM)	n (%)	
		Alirocumab	Control
Nasopharyngitis	BM	122 (10.6)	65 (10.7)
	AM	154 (13.2)	72 (12.2)
Upper respiratory tract infection	BM	92 (8.0)	50 (8.2)
	AM	84 (7.2)	53 (9.0)
Influenza	BM	69 (6.0)	35 (5.7)
	AM	64 (5.5)	34 (5.8)
Injection site reaction	BM	53 (4.6)	23 (3.8)
	AM	88 (7.5)	32 (5.4)
Back pain	BM	59 (5.1)	36 (5.9)
	AM	64 (5.5)	36 (6.1)
Diarrhea	BM	59 (5.1)	36 (5.9)
	AM	58 (5.0)	22 (3.7)
Arthralgia	BM	64 (5.6)	36 (5.9)
	AM	63 (5.4)	37 (6.3)
Headache	BM	65 (5.7)	43 (7.1)
	AM	56 (4.8)	26 (4.4)
Myalgia	BM	54 (4.7)	22 (3.6)
	AM	59 (5.0)	23 (3.9)
Urinary tract infection	BM	46 (4.0)	39 (6.4)
	AM	61 (5.2)	33 (5.6)
Bronchitis	BM	46 (4.0)	33 (5.4)
	AM	61 (5.2)	30 (5.1)
Dizziness	BM	39 (3.4)	28 (4.6)
	AM	48 (4.1)	30 (5.1)

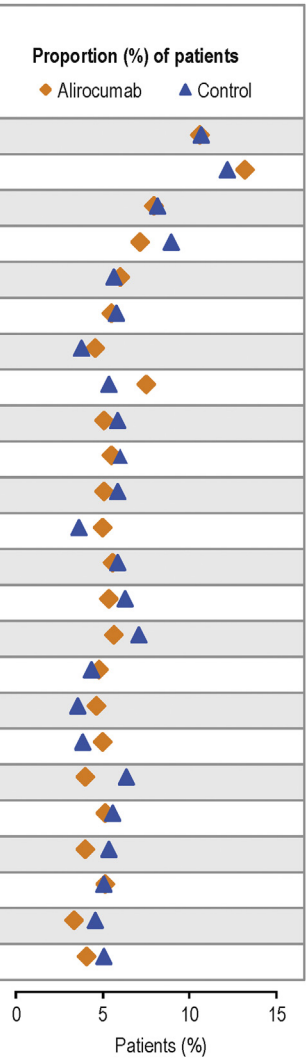

Figure 5 Adverse events by baseline total PCSK9 levels below or at/above the median. Pooled data from LONG TERM, COMBO II, FH I, and MONO studies. Total number of patients per group: alirocumab, below median, N = 1147, at/above median, N = 1170; control, below median N = 609, at/above median N = 590. TEAE, treatment-emergent adverse event.

FH. There was a corresponding increase in total PCSK9 levels reflecting increased levels of the inactive PCSK9:alirocumab complex. These results confirm those of alirocumab phase 1 and 2 trials[4–6]; however, the present analysis is the first to report pharmacokinetic and PCSK9 data for the 75 mg Q2W dose and following dose increase to 150 mg Q2W. As seen in previous studies, total PCSK9 levels were higher at the baseline compared with free PCSK9 levels; however, it is not clear what endogenous elements may be binding PCSK9 in serum. After alirocumab administration, all but the most insignificant amount of total PCSK9, not accounted for by the free PCSK9 assay, is bound to alirocumab. The difference between free and total PCSK9 at the baseline is not currently well understood.

Three of the trials in this analysis allowed for alirocumab dose increase at week 12 based on week 8 LDL-C.[7–9] Dose increase was associated with a further reduction in free PCSK9 levels and a corresponding further reduction in LDL-C; however, the additional LDL-C reduction after dose increase in MONO was relatively small compared with FH I and COMBO II. One explanation for this may be the lower baseline PCSK9 levels observed in patients from MONO, who were not receiving background statin therapy, compared with the other studies in which patients were receiving background maximally tolerated statin. The higher levels of PCSK9 in the statin-treated patients may be accounted for by the statin-induced increased production of PCSK9 via upregulation of sterol-responsive element-binding protein 2.[2] If most of the free PCSK9 is already bound to alirocumab in patients receiving the 75 mg Q2W dose (ie, the system is fully saturated), this could explain why increasing the alirocumab dose had only minimal effects on LDL-C in the patients not on statin from MONO. However, the efficacy of alirocumab was found to be consistent in patients with baseline free PCSK9 above or below the median. In MONO and COMBO II, patients with dose increase had a lower percentage LDL-C reduction at week 24 compared with patients with no dose increase. An

explanation for this is that patients with a lower percentage reduction were more likely to not reach the LDL-C goal at week 8 and therefore were more likely to have their dose increased (in FH I, percent reductions were similar at week 24 regardless of dose increase status).

Baseline LDL-C levels were higher in patients who required alirocumab dose increase (vs no dose increase) in all studies, in agreement with previous analyses showing that baseline LDL-C levels are the main determining factor for requiring alirocumab dose increase.[19] Overall, 51.2% of patients from MONO, COMBO II, and FH I with baseline LDL-C ≥130 mg/dL received a dose increase. Baseline free PCSK9 levels were also somewhat higher in patients who required dose increase (vs no dose increase) in MONO and COMBO II, although this was not true for FH I. However, baseline PCSK9 levels were highest overall in FH I vs the other trials, in agreement with previous reports of elevated PCSK9 levels in patients with FH.[20]

There have been some reports of resistance to PCSK9 mAbs. In one study, two patients with FH (confirmed by clinical criteria) were reported to have a lack of LDL-C response, either despite an increase in total PCSK9 levels (suggesting alirocumab had bound to PCSK9 in the circulation) or with a lack of increase in total PCSK9 (that may suggest lack of alirocumab binding to PCSK9 or that alirocumab did not enter the circulation in sufficient levels).[21] In an analysis of patients who participated in alirocumab ODYSSEY trials, a small number of patients randomized to alirocumab (<1%) who had <15% LDL-C reduction were identified, but in most of these patients, nonadherence was felt to explain the lack of response.[22] For a few patients with lack of response, alirocumab receipt was confirmed by PK analysis, with a corresponding decrease in free PCSK9 and an increase in total PCSK9. Such cases may suggest a mutation or mutations in the *LDLR* and/or *APOB* genes that reduce uptake of LDL-C from the circulation (thus interfering with the mode of action of PCSK9 inhibition with alirocumab). In some of the patients with lack of LDL-C response in the ODYSSEY trials, *LDLR* mutations were identified; however, other patients with the same mutations did show a response.[22] A further analysis of genetically profiled patients with either double or compound heterozygous *LDLR* and/or *APOB* mutations found that the LDL-C response (reduction from baseline) ranged from 8.8% to 65.1% with alirocumab.[23]

In the trials included in this analysis, alirocumab was generally well tolerated with safety comparable with controls (except for a higher frequency of injection site reactions with alirocumab). These results are in agreement with a pooled safety analysis of alirocumab phase 2 and 3 trials as well as results from the ODYSSEY OUTCOMES CV outcomes trial.[24,25]

In summary, alirocumab-induced changes in PCSK9 and LDL-C concentrations in this analysis were consistent with the known physiologic relationship between concentrations of PCSK9, LDL receptor, and LDL-C, as well as statin-induced increases in PCSK9 production. Taken together, these analyses provide further support for the use of alirocumab 75 mg Q2W and dose increase to 150 mg Q2W (based on LDL-C levels) as efficacious dosing regimens for clinically meaningful LDL-C reductions in patients with hypercholesterolemia receiving maximally tolerated statin therapy.

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Appendix

Supplementary Table 1 Study and baseline characteristics (randomized population)

	MONO (n = 103)	COMBO II (n = 720)	FH I (n = 486)	LONG TERM (n = 2341)
Patient characteristics at the baseline				
Mean age, years (SD)	60.2 (5.0)	61.6 (9.3)	51.9 (12.7)	60.5 (10.4)
Male gender, n (%)	55 (53.4)	530 (73.6)	274 (56.4)	1457 (62.2)
Race/ethnicity white, n (%)	93 (90.3)	610 (84.7)	444 (91.4)	2171 (92.7)
Mean BMI (SD)	29.3 (6.3)	30.1 (5.3)	29.3 (4.9)	30.3 (5.6)
ASCVD, n (%)	0	685 (95.1)	235 (48.4)	1799 (76.8)
CHD, n (%)	N/A	649 (90.1)	225 (46.3)	1607 (68.6)
CHD associated with >1 comorbidity* or CVD†	N/A	544 (75.6)	147 (30.2)	1294 (55.3)
CHD risk equivalents‡	N/A	233 (31.0)	79 (16.3)	962 (41.1)
Mean SCORE (SD)§	2.8 (1.2)	N/A	N/A	N/A
Familial hypercholesterolemia, n (%)	0	0	486 (100)	415 (17.7)
High-intensity statin‖, n (%)	0	480 (66.7)	396 (81.5)	1032 (44.1)
Non-statin LLT, n (%)	5 (4.9)	41 (5.7)¶	305 (62.8)¶	657 (28.1)¶
Mean LDL-C, mg/dL (SD)	139.7 (25.8)	107.3 (35.7)	144.6 (49.7)	122.4 (42.2)

ALI, alirocumab; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; N/A, not applicable; PBO, placebo; PCSK9, proprotein convertase subtilisin/kexin type 9; SCORE, Systematic Coronary Risk Estimation; SD, standard deviation.

*Comorbidity includes hypertension, diabetes or moderate chronic kidney disease.

†CVD includes ischemic stroke and peripheral arterial disease.

‡Includes ischemic stroke, peripheral arterial disease, moderate chronic kidney disease, known history of diabetes and (2) additional risk factors.

§MONO study excluded patients with CHD. Only those with moderate CV risk, as assessed using Systematic Coronary Risk Estimation (SCORE), were included.

‖Defined as atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily.

¶With or without statin.

Supplementary Table 2 Alirocumab dose adjustment status at week 12 according to baseline calculated LDL-C levels (ITT population; pool of alirocumab-treated patients from MONO, COMBO II, and FH I)

	Calculated LDL-C at the baseline			
n (%)	≤100 mg/dL	≥100 to <130 mg/dL	≥130 to <160 mg/dL	≥160 mg/dL
N	n = 268	n = 232	n = 165	n = 138
Dose adjustment from 75 mg Q2W to 150 mg Q2W at week 12	24 (9.0)	52 (22.4)	68 (41.2)	87 (63.0)

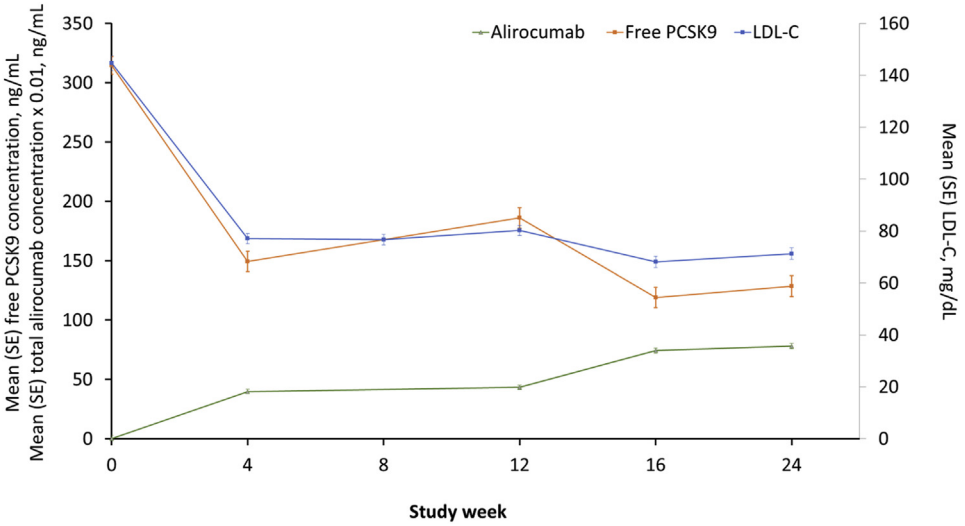
ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 wk.

Patients who prematurely discontinued the study treatment before week 12 are excluded from this analysis.

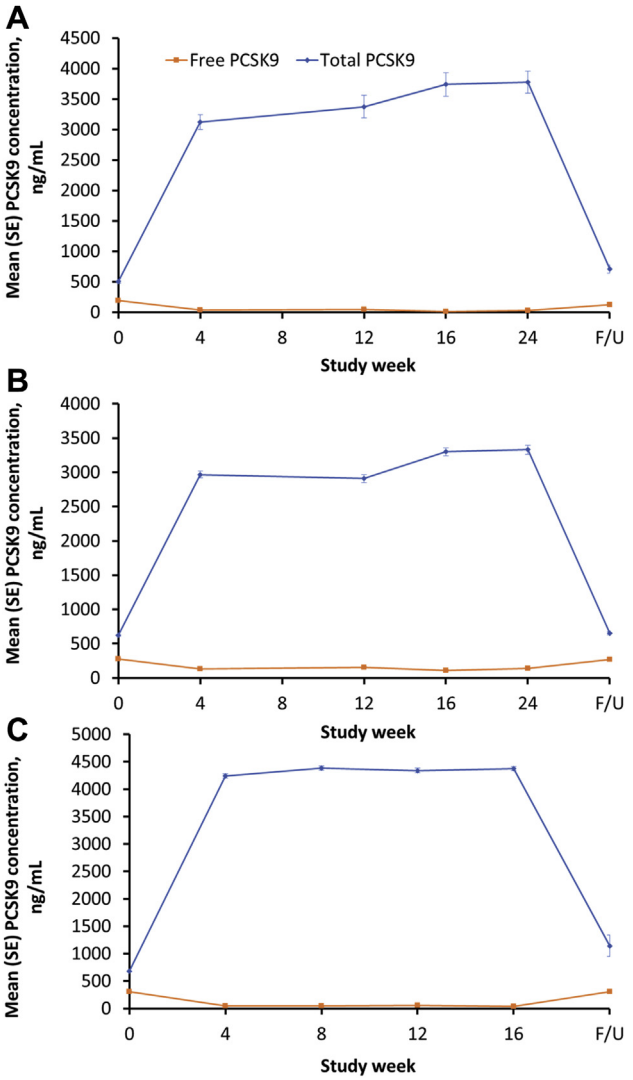
Supplementary Table 3 Safety summary (safety population)

	Placebo-controlled trials Pool of FH I and LONG TERM		Ezetimibe-controlled trials Pool of COMBO II and MONO	
Values are n (%)	Alirocumab (n = 1872)	Placebo (n = 951)	Alirocumab (n = 531)	Ezetimibe (n = 292)
TEAEs	1518 (81.1)	779 (81.9)	427 (80.4)	238 (81.5)
Treatment-emergent SAEs	334 (17.8)	176 (18.5)	125 (23.5)	61 (20.9)
TEAEs leading to death	14 (0.7)	10 (1.1)	6 (1.1)	6 (2.1)
TEAEs leading to discontinuation	122 (6.5)	56 (5.9)	49 (9.2)	23 (7.9)
TEAEs in ≥5% of patients				
Nasopharyngitis	245 (13.1)	115 (12.1)	35 (6.6)	23 (7.9)
Upper respiratory tract infection	137 (7.3)	82 (8.6)	44 (8.3)	22 (7.5)
Injection site reaction	131 (7.0)	51 (5.4)	13 (2.4)	5 (1.7)
Influenza	108 (5.8)	55 (5.8)	28 (5.3)	19 (6.5)
Arthralgia	102 (5.4)	61 (6.4)	28 (5.3)	12 (4.1)
Back pain	103 (5.5)	60 (6.3)	21 (4.0)	13 (4.5)
Headache	91 (4.9)	54 (5.7)	33 (6.2)	15 (5.1)
Urinary tract infection	103 (5.5)	59 (6.2)	10 (1.9)	13 (4.5)
Bronchitis	93 (5.0)	50 (5.3)	18 (3.4)	14 (4.8)
Diarrhea	100 (5.3)	50 (5.3)	20 (3.8)	10 (3.4)
Myalgia	90 (4.8)	34 (3.6)	27 (5.1)	14 (4.8)
Hypertension	70 (3.7)	39 (4.1)	33 (6.2)	15 (5.1)
Dizziness	57 (3.0)	38 (4.0)	31 (5.8)	21 (7.2)
Accidental overdose	21 (1.1)	14 (1.5)	48 (9.0)	20 (6.8)

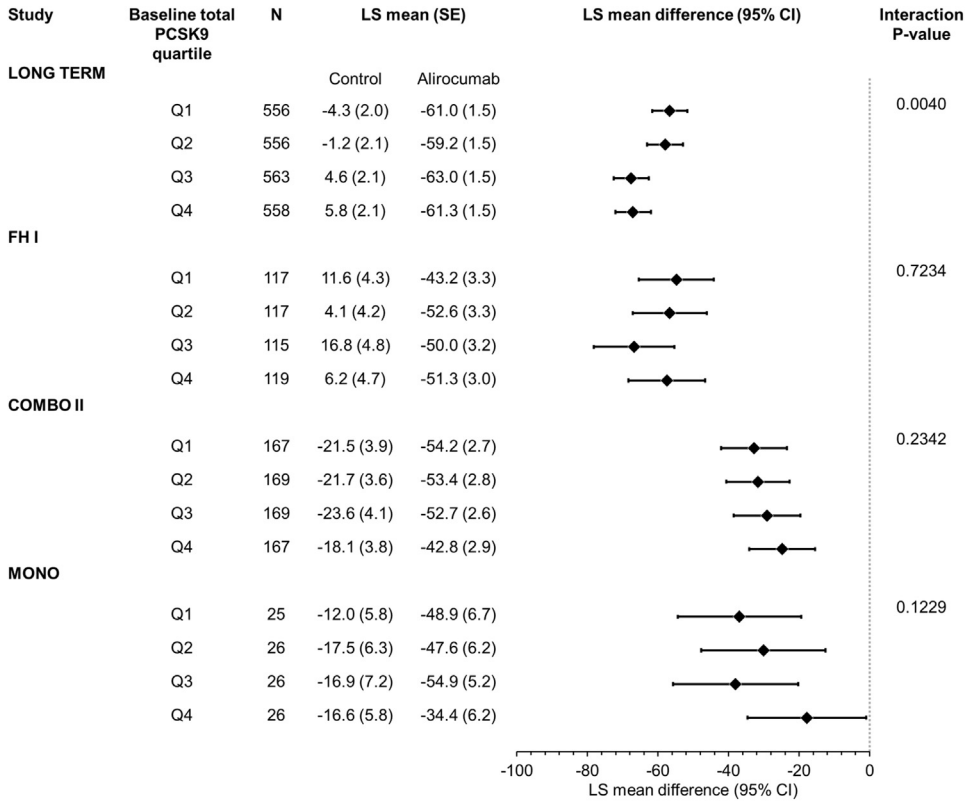
SAE, serious adverse event; TEAE, treatment-emergent adverse event.



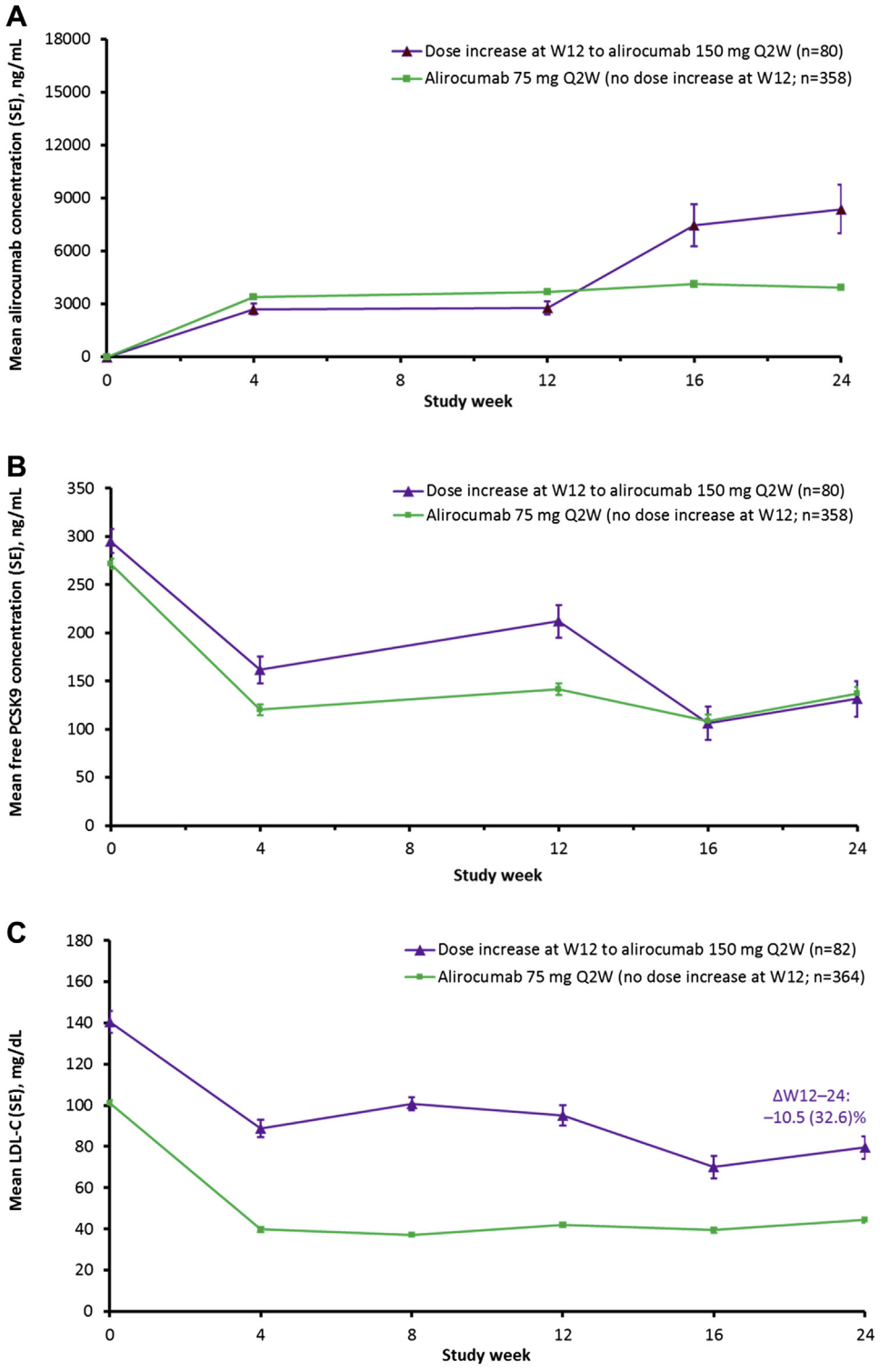
Supplementary Figure 1 Mean concentrations of alirocumab, free PCSK9 and LDL-C over time in patients with HeFH receiving alirocumab 75/150 mg Q2W with background statin (FH I). HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 wk; SE, standard error.



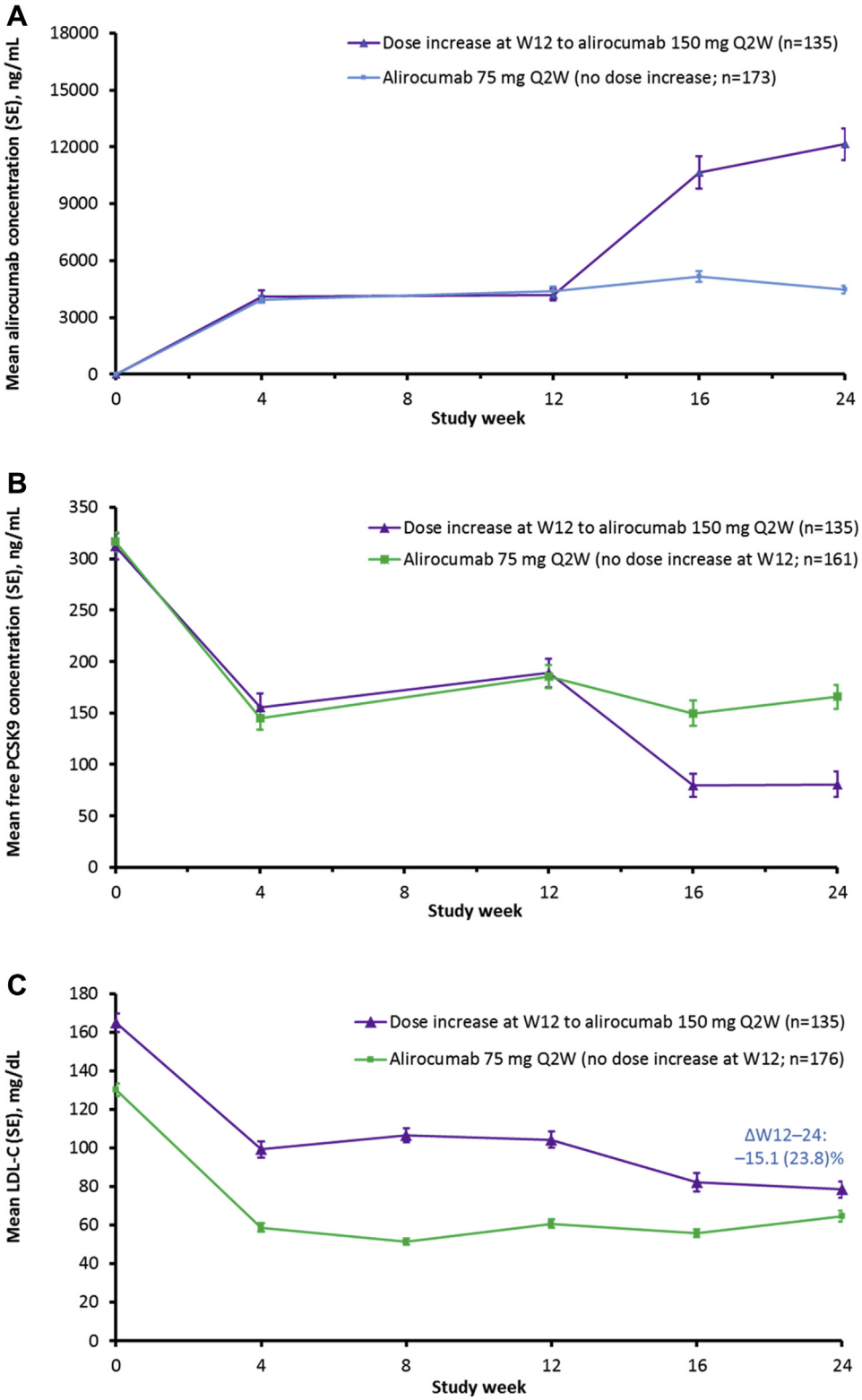
Supplementary Figure 2 Free and total PCSK9 concentrations after treatment with (A) alirocumab 75/150 mg Q2W (MONO; no background statin), (B) alirocumab 75/150 mg Q2W (COMBO II; background statin), and (C) alirocumab 150 mg Q2W (LONG TERM; background statin) (alirocumab-treated patients). Follow-up was at 32 wk in MONO, 112 wk in COMBO II, and 86 wk in LONG TERM. PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 wk; SE, standard error; F/U, follow-up.



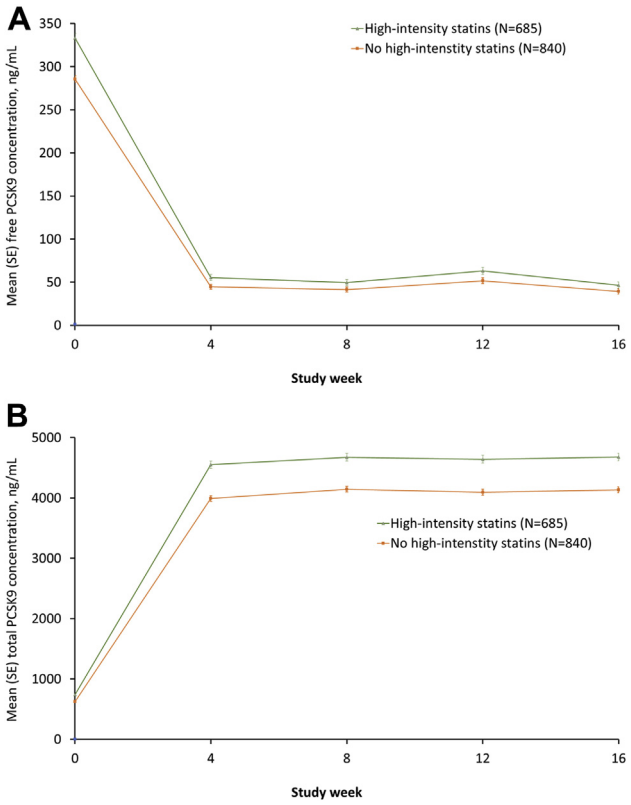
Supplementary Figure 3 LDL-C percentage reduction at week 24 according to quartiles of baseline total PCSK9 levels. The interaction *P*-values compare quartile 1 with quartile 4. CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least-squares; PCSK9, proprotein convertase subtilisin/kexin type 9; SE, standard error.



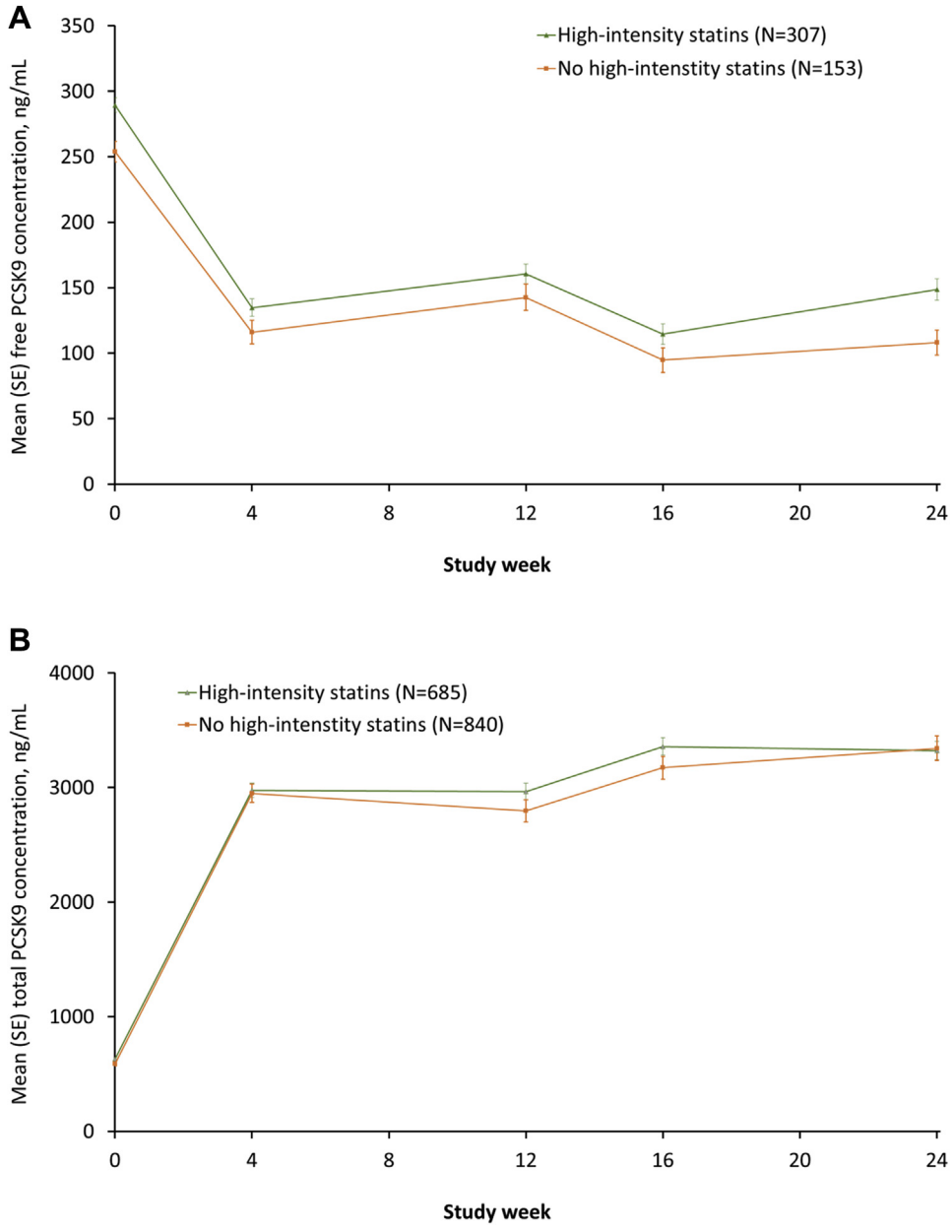
Supplementary Figure 4 Effect of alirocumab dose increase from 75 to 150 mg Q2W on mean concentrations of (A) alirocumab, (B) free PCSK9 and (C) LDL-C over time, in alirocumab-treated patients from the COMBO II study (with background statin) LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 wk; SE, standard error.



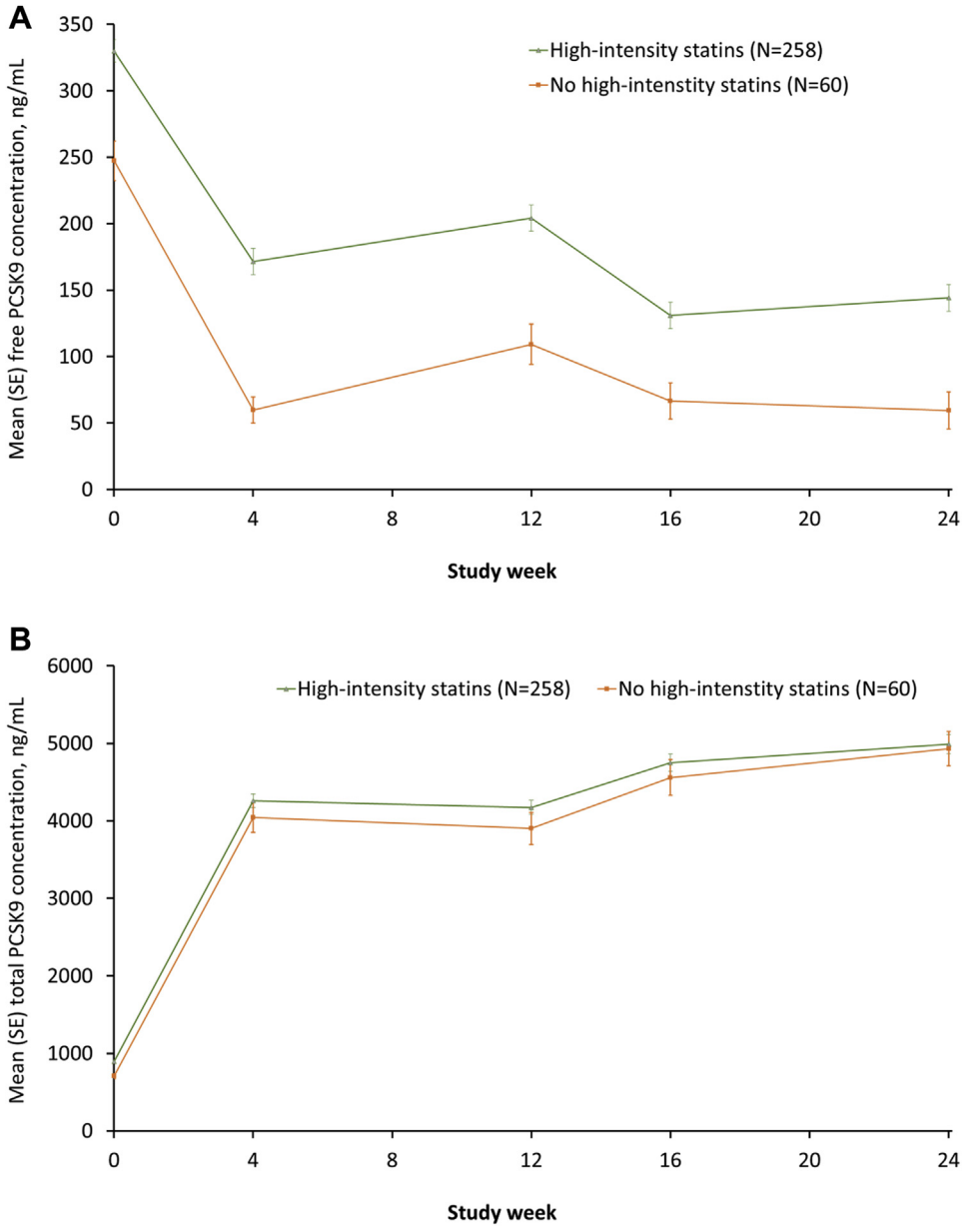
Supplementary Figure 5 Effect of alirocumab dose increase from 75 to 150 mg Q2W on mean concentrations of (A) alirocumab, (B) free PCSK9 and (C) LDL-C over time, in alirocumab-treated patients from the FH I study (with background statin). LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 wk; SE, standard error.



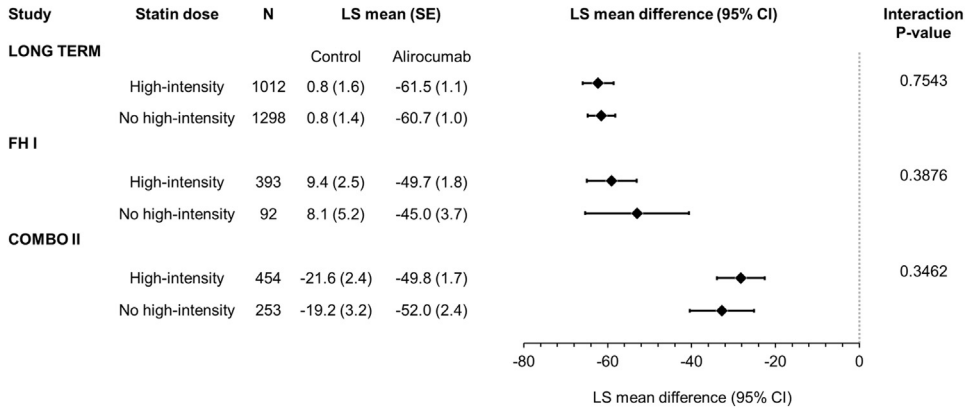
Supplementary Figure 6 Free (A) and total (B) PCSK9 levels by statin dose intensity in LONG TERM (alirocumab-treated patients). High-intensity statin was defined as atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily. PCSK9, proprotein convertase subtilisin/kexin type 9; SE, standard error.



Supplementary Figure 7 Free (A) and total (B) PCSK9 levels by statin dose intensity in COMBO II (alirocumab-treated patients). High-intensity statin was defined as atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily. PCSK9, proprotein convertase subtilisin/kexin type 9; SE, standard error.



Supplementary Figure 8 Free (A) and total (B) PCSK9 levels by statin dose intensity in FH I (alirocumab-treated patients). High-intensity statin was defined as atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily. PCSK9, proprotein convertase subtilisin/kexin type 9; SE, standard error.



Supplementary Figure 9 LDL-C percentage reduction at week 24 according to statin dose intensity. High-intensity statin was defined as atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily. LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error.